IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF TEXAS
Fort Worth Division

FARMAKEIO OUTSOURCING, LLC, Plaintiff, v. UNITED STATES FOOD AND DRUG ADMINISTRATION; and DR. ROBERT M. CALIFF, in his official capacity as Commissioner of Food and Drugs, 10903 New Hampshire Ave., Silver Spring, Maryland 20903 Defendants.	Civil Action No. 4:24-cv-1040

COMPLAINT

Plaintiff FarmaKeio Outsourcing, LLC ("FarmaKeio Outsourcing"), by and through undersigned counsel, alleges as follows:

Nature of the Action

1. FarmaKeio Outsourcing brings this action to challenge unlawful action by the Food and Drug Administration in placing corporate profits and its own policy preferences ahead of patient needs and physicians' clinical judgment. In 2013, Congress passed a law expressly authorizing bulk drug compounding by manufacturers known as "outsourcing facilities." Compounding is the process by which a doctor, pharmacist, or outsourcing facility combines, mixes, or alters ingredients to create medicines tailored to patient needs, as determined by a physician's clinical judgment. That law established a comprehensive regulatory regime designed to meet patients' clinical needs through bulk drug compounding while ensuring safety. To that end, Congress generally authorized outsourcing facilities to compound from bulk drug substances for which there is a "clinical need" and directed FDA to maintain a list of substances satisfying that criterion.

2. Consistent with its longstanding disfavor of drug compounding, FDA has resisted that mandate. In the decade since Congress ordered it to establish the clinical-need list of drug substances that may be compounded by outsourcing facilities, the agency has listed a sum-total of five drug substances, all of them since 2022 and all of them subject to extra-statutory restrictions—for example, limiting compounded products to those intended for topical use only. Meanwhile, the agency has rejected 22 drug substances. That lopsided result is a consequence of FDA's interpretation of the statutory term "clinical need" to encompass a host of factors that have nothing to do with clinical need. Whereas Congress directed FDA to consider whether drug substances are needed in clinical treatment—the plain meaning of the statutory term—FDA rejects drug substances based on irrelevant considerations including how compounded versions might compare to existing drug products approved under its preferred "new drug" regulatory regime. The agency has openly admitted that it adopted this approach to influence the "economic incentives" of companies deciding whether "to seek FDA approval" under the "new drug" regime, as opposed to compounding. The agency's approach to "clinical need" is not only unmoored from the statutory text, but opposed to it: the need for a drug substance in clinical treatment now has little bearing on the determination of "clinical need."

3. This case concerns sodium thiosulfate, an active ingredient that treats severe medical conditions including cyanide poisoning and calciphylaxis. The "clinical need" for sodium thiosulfate is straightforward: the ingredient is needed in clinical treatment. It has been proven safe and effective for treating severe medical conditions, and it is in demand in medical settings across the United States.

4. FDA, however, determined that there is no clinical need for the ingredient. That determination was not based on any assessment of "clinical need" in the statutory sense but on FDA's impression that commenters had not proven that drugs compounded from that substance

are somehow superior to FDA-approved drugs. In applying that test, FDA places a heavy presumption in favor of the FDA-approved drugs that is in practice nearly insurmountable.

5. FDA has interpreted the statute incorrectly, to the detriment of patients and physicians. Congress acted to make compounded versions of drugs available based on clinical need. But FDA believes Congress ought to have erected a higher standard to limit compounding and subject more drug products that might otherwise be compounded to FDA approval as "new drugs." The FDA has no authority to override Congress. The Court's intervention is required to set the agency straight, restore the compounding-friendly system that Congress enacted, set aside FDA's unlawful rejection of sodium thiosulfate, and ensure that patients have access to high-quality and affordable compounded products that their physicians have determined are needed for their treatment.

Parties

6. FarmaKeio Outsourcing is a Texas limited-liability company with its principal place of business in Southlake, Texas. FarmaKeio Outsourcing is an outsourcing facility registered under § 503B of the Federal Food, Drug, and Cosmetic Act (FDCA). In compliance with § 503B, it compounds drugs, including from bulk ingredients, under the conditions of § 503B and in circumstances where such compounding is lawful under that provision.

7. Defendant FDA is a federal agency of the United States Government headquartered in Silver Spring, Maryland. It is an agency for purposes of the APA and is subject to its requirements.

8. Defendant Dr. Robert M. Califf is the Commissioner of Food and Drugs and is named in his official capacity only.

Jurisdiction and Venue

9. This Court has jurisdiction under 28 U.S.C. § 1331. Through the APA, the United States has waived sovereign immunity from this lawsuit. *See* 5 U.S.C. § 702.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(e) because Plaintiff FarmaKeio Outsourcing is a resident of this district, and a substantial part of the events or omissions giving rise to the claim occurred in this district, where FDA's action is directly regulating Plaintiff FarmaKeio Outsourcing.

Factual and Legal Background

Congress Legislates to Ensure Safe and Effective Compounded Drugs Can Meet Patient Needs

11. "Drug compounding is a process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication," typically one that is "not commercially available, such as medication for a patient who is allergic to an ingredient in a mass-produced product." *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 360–61 (2002). For about 50 years after the FDCA was enacted in 1938, "the FDA generally left regulation of compounding to the States." *Id.* at 362.

12. However, in 1992 FDA announced that it would deem compounded drugs manufactured and sold in large quantities as within the FDCA's ambit and that only compounding meeting various factors—such as that it occur "after receipt of a valid prescription for an individual patient" and "in 'very limited quantities'"—would be permitted without new-drug approval. *Id.* at 363 (quoting Compliance Policy Guide 7132.16).

13. In response, Congress enacted the Food and Drug Administration Modernization Act (FDAMA) of 1997, codified as FCDA § 503A, 21 U.S.C. § 353a. The law exempted compounded drugs from the FDCA's new drug requirements if they satisfied multiple restrictions, including that compounding occur in response to a prescription and in limited quantities. *Id.* at 364.

14. Congress subsequently enacted the Drug Quality and Security Act (DQSA), Pub. L. No. 113-54, 127 Stat. 587 (2013). The DQSA added a new FDCA provision, § 503B, 21 U.S.C. § 353b, that exempts certain "bulk" drug compounding from the new-drug approval process

(among other FDCA strictures) and comprehensively regulates such compounding. Congress did not ban compounding drugs in large quantities, but expressly permitted it, subject to regulation.

15. The DQSA recognizes "outsourcing facilities" and subjects them to registration, inspection, and reporting requirements and other regulations. *See id.* § 353b(a)(1) and (b). Outsourcing facilities need not be registered pharmacies or obtain prescriptions for identified patients as a prerequisite to compounding. *Id.* § 353b(d)(4)(B) and (C).

16. The statute formally exempts from the new-drug approval process "a drug compounded … in a facility that elects to register as an outsourcing facility if each of" a list of conditions are satisfied. *Id.* § 353b(a).

17. One of the conditions is that the "outsourcing facility … does not compound using bulk drug substances …, unless … the bulk drug substance appears on a list established by the Secretary identifying bulk drug substances for which there is a clinical need" through a notice-and-comment process. *Id.* § 353b(a)(2)(A)(i) (the "Clinical Need Condition"). The Clinical Need Condition further requires FDA to publish "a notice in the Federal Register proposing bulk drug substances to be included on the list" of those for which there is a clinical need and another notice "designating bulk drug substances for inclusion on the list." 21 U.S.C. § 353b(a)(2)(A)(i)(I) and (III).

18. The Clinical Need Condition is unambiguous in requiring FDA to make a straightforward determination whether a "bulk drug substance" is one "for which there is a clinical need." The term "bulk drug substance" is defined to refer to an "active pharmaceutical ingredient," not a finished drug. 21 U.S.C. § 353b(a)(2) (incorporating 21 C.F.R. § 207.3); *see also* 21 C.F.R. § 207.1. FDA's task is not to determine whether there is a clinical need for a finished drug or a compounded version of a drug, but simply whether there is a clinical need for an active ingredient.

19. The term "clinical need" is satisfied if an active ingredient is needed in clinical treatment.

20. FDA's task, then, in administering the Clinical Need Condition is to compile a list of active ingredients that are needed in clinical treatment in the United States. Where a bulk drug substance is an active ingredient in an approved drug that FDA has already determined is safe and effective, and is in current or historical demand in clinical treatment, FDA has no discretion to determine that there is not a clinical need for that substance.

FDA Replaced the Clinical Need Inquiry with an Inquiry Aimed at Restricting Bulk Compounding

21. FDA has applied the DQSA more as a ban than a regulation. Rather than list bulk drug substances for which there is a need in clinical treatment, FDA did nothing for nearly a decade and then has spent the past several years *excluding* active ingredients from the list.

22. FDA has created a regulatory approach to assessing "clinical need" that clashes with Congress's design. FDA's approach is set forth in "guidance" it finalized in 2019, which it has implemented in its actions administering the Clinical Need Requirement since then. *See Evaluation of Bulk Drug Substances Nominated for Use in Compounding Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (Clinical Need Guidance).[1]

23. From the two words "clinical need," FDA has inferred a series of "critical safeguards" to "help[] ensure outsourcing facilities do not operate like conventional manufacturers of unapproved new drug products." *Id.* at 9. In other words, rather than treat "clinical need" as a patient-focused inquiry concerning what ingredients are needed in clinical treatment, FDA has read it as a bureaucratic term that prioritizes FDA's preferred regulatory regime and regulatory power over Congress's general approval of bulk compounding.

[1] *Available at* https://www.fda.gov/media/121315/download (last accessed October 25, 2024).

24. The FDA's elaborate, multi-step inquiry is the very opposite of what the statutory text requires. To begin with, the Clinical Need Guidance bifurcates the singular phrase "clinical need" into "a two-part analysis" for assessing its proposed inquiry of "whether there is a clinical need for outsourcing facilities to compound using the bulk drug substance." *Id.* at 10. The first part "determine[s] whether the bulk drug substance is a component of an FDA-approved product." *Id.* at 11.

25. The statutory Clinical Need Condition imposes one standard, not two. But FDA imposes different standards in assessing drug substances that are components of FDA-approved products from those that are not components of FDA-approved products.

26. If the substance is a component of an FDA-approved product, FDA will determine, *inter alia*, whether "an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation" and whether "there a basis to conclude that the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product." *Id.* at 11.

27. This defies statutory text. The Clinical Need Condition calls for an inquiry into whether there is a "clinical need" for an active ingredient, rather than for the compounding of a finished product.

28. FDA also defies text by asking whether compounding is a superior form of producing the drug by comparison to an FDA-approved form.

29. If a substance that is a component of an FDA-approved drug satisfies the first set of inquiries, or is not a component of an FDA-approved drug, then FDA proceeds to consider still more factors, including: "(a) The physical and chemical characterization of the substance; (b) Any safety issues raised by the use of the substance in compounding; (c) The available evidence of effectiveness or lack of effectiveness of a drug product compounded with the substance, if any

such evidence exists; and (d) Current and historical use of the substance in compounded drug products, including information about the medical condition(s) that the substance has been used to treat and any references in peer-reviewed medical literature." *Id.* at 11–12.

30. Under factor (a), FDA will "determine whether the substance can be identified or compounded consistently based on its physical and chemical characteristics." *Id.* at 14.

31. Under factor (b), FDA will determine, *inter alia*, whether alternative "approved drug products or OTC drug products would" serve needs to be served by a compounded drug. *Id.* at 15.

32. Under factor (c), FDA will consider whether substances "have been widely used for a long period of time," whether "the literature … include[s] anecdotal reports of effectiveness," and whether there are alternative "drug products approved to treat the [relevant] condition." *Id.* at 16.

33. Under factor (d), FDA will "consider the historical and current use of the substance in compounding drug products." *Id.* at 17.

34. In administering these criteria, too, FDA compares the prospect of compounded finished drugs from the substance against FDA-approved drugs containing the substance. It does not ask, as the Clinical Need Condition directs, simply whether the active ingredient itself is needed in clinical treatment.

35. In summary, the FDA has replaced the straightforward inquiry required by the statutory text with two overlapping multi-factor inquiries designed to restrict compounding in favor of the FDA's preferred "new drug" regulatory regime.

36. The consequence, unsurprisingly, is that substances that are components of FDA-approved drugs practically never qualify for inclusion on the list of ingredients for which there is a clinical need.

FDA Declines To List Sodium Thiosulfate Even Though It Is Needed in Clinical Treatment

37. Sodium thiosulfate an inorganic sodium salt composed of sodium and thiosulfate ions. It is a critically important bulk drug substance that is an antidote to cyanide poisoning. It was nominated for inclusion on the clinical need list for the treatment of calciphylaxis, cyanide toxicity, extravasation, Malassezia furfur, and nephrotoxicity prophylaxis. All of these are severe medical conditions.

38. Sodium thiosulfate is safe and effective in treating these conditions, and it is (and has been historically) in demand in clinical treatment.

39. There is a clinical need for sodium thiosulfate. Under a proper interpretation and administration of the Clinical Need Condition, sodium thiosulfate would qualify for the clinical-need list.

40. However, sodium thiosulfate is a component of an FDA-approved drug. Accordingly, under the atextual gauntlet FDA created, FDA's rejection of sodium thiosulfate was virtually preordained.

41. On January 27, 2022, FDA issued a notice of final agency action in the Federal Register addressing, *inter alia*, eight bulk drug substances that are components of FDA-approved drugs, including sodium thiosulfate. List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act, 87 Fed. Reg. 4240 (the "Rejection Action"). FDA determined that none of these substances qualified for inclusion on the list (with a partial exception explained below).

42. As relevant here, sodium thiosulfate did not qualify for inclusion on the clinical-need list, except that FDA left open the possibility that it *might* qualify "for topical administration." *Id.* at 4240. As for topical administration, FDA announced that "topical administration" of sodium thiosulfate "only remains under consideration by the Agency at this time." *Id.* at 4250. FDA

rejected all other possible uses, applications, and dosages of sodium thiosulfate for inclusion on the clinical-need list.

43. In evaluating sodium thiosulfate, FDA applied the framework set forth in its Clinical Need Guidance.

44. Specifically, FDA compared compounding of sodium thiosulfate against the FDA-approved drug that contains that active ingredient and demanded proof that "an attribute of the FDA-approved drug product makes it medically unsuitable to treat certain patients for a condition that FDA has identified for evaluation," that "the drug product proposed to be compounded is intended to address that attribute," and that "the drug product proposed to be compounded must be produced from a bulk drug substance rather than from an FDA-approved drug product." *Id.* at 4242.

45. FDA did not undertake an inquiry into whether there is a clinical need for sodium thiosulfate, the ingredient itself.

46. FDA broke down its analysis of sodium thiosulfate further by assessing these factors for each proposed use—i.e., for calciphylaxis, cyanide toxicity, extravasation, and nephrotoxicity prophylaxis. But the Clinical Need Condition does not ask FDA to determine what specific uses there are for an active ingredient, only whether there is "*a* clinical need" for it. 21 U.S.C. § 353b(a)(2)(A)(i) (emphasis added).

47. The Clinical Need Condition does not direct FDA to approve or disapprove uses, doses, or applications of an active ingredient. Yet FDA claims the authority to do so in administering the clinical-need list.

48. FDA considered comments presenting evidence that a compounded form of sodium thiosulfate would overcome deficiencies in the FDA-approved product. FDA placed a heavy

burden on the proponents of listing to establish unsuitability of the FDA-approved product. It found that burden unmet in each instance.

49. For example, FDA dismissed a comment "that it may be necessary to compound a product with a greater concentration than is commercially available" simply by noting that "the nomination does not identify specific higher concentrations that the nominator proposes to compound or provide any data or information supporting the need for a higher concentration." 87 Fed. Reg. at 4249.

50. As another example, FDA dismissed a comment proposing "to combine sodium thiosulfate with sodium nitroprusside to reduce the risk of cyanide toxicity during sodium nitroprusside administration" on the basis that it "does not identify the final product formulation proposed to be compounded (e.g., dosage form and strength of each ingredient)." *Id.*

51. Further, in response to a comment that "a combined compounded preparation would allow for faster administration in the clinical setting and fewer human manipulations, thus reducing the rate of error," FDA stated that it does "not consider the risk that a clinician may mishandle the approved product to be an indicator of clinical need." *Id.*

52. Applying this approach, FDA rejected every contention in favor of listing (save one partial exception) and rejected every proposed use of a finished compounded drug containing sodium thiosulfate. *Id.* at 4249–50. FDA found "no basis to conclude that an attribute of the FDA-approved products makes them medically unsuitable to treat certain patients and that the proposed compounded drug products are intended to address." *Id.* at 4250. It therefore did "not consider whether there is a basis to conclude that the drug products proposed to be compounded must be prepared using a bulk drug substance rather than an FDA-approved drug product." *Id.* It did not consider any additional factors.

53. FDA conducted no inquiry into whether there is a clinical need for sodium thiosulfate. It did not examine whether the active ingredient sodium thiosulfate is safe, effective, and in current or historical demand for clinical treatment.

54. The one partial exception to its determination, as noted, is that FDA continues to consider whether a compounded form of sodium thiosulfate is appropriate for topical administration. FDA did not approve sodium thiosulfate for topical administration; it simply announced that it continues to consider this application. Over two years later, FDA still has not decided whether sodium thiosulfate is appropriate for topical administration.

55. This only confirms FDA's incorrect administration of the Clinical Need Condition. FDA is not directed to pick and choose applications of active ingredients, only to determine whether there is a clinical need for them.

FarmaKeio Outsourcing Is Barred from Compounding Sodium Thiosulfate

56. FarmaKeio Outsourcing owns and operates an outsourcing facility in Southlake, Texas, that is registered under § 503B of the FDCA.

57. FarmaKeio Outsourcing complies with all requirements of § 503B and currently engages in lawful compounding under FDA's supervision. This includes compliance with reporting and inspection requirements, as well as good manufacturing practice under the FDCA.

58. Because sodium thiosulfate does not appear on the list required under the Clinical Need Condition, or the separate drug shortage list, it is ineligible for compounding by FarmaKeio Outsourcing.

59. FarmaKeio Outsourcing is willing and able to compound sodium thiosulfate at its outsourcing facility. But for FDA's final decision declining to list sodium thiosulfate, FarmaKeio Outsourcing would compound from sodium thiosulfate at its outsourcing facility.

60. FDA's final action declining to list sodium thiosulfate therefore directly injures FarmaKeio Outsourcing.

FIRST CAUSE OF ACTION
(Unlawful and Arbitrary Agency Action in Violation of the Administrative Procedure Act)

61. The above paragraphs are hereby incorporated by reference as if set forth fully herein.

62. The APA provides for judicial review of "final agency action for which there is no other adequate remedy." 5 U.S.C. § 704. FDA's decision not to reject inclusion of sodium thiosulfate on the clinical need list is final agency action for which there is no other adequate remedy.

63. FDA's decision not to include sodium thiosulfate on the clinical need list "is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A). Section 503B of the FDCA requires FDA to create "a list … identifying bulk drug substances for which there is a clinical need." 21 U.S.C. § 353b(a)(2)(A)(i).

64. FDA's administration of the Clinical Need Condition is unlawful because it is not in accordance with the FDCA.

65. FDA's application of its approach to sodium thiosulfate is unlawful and arbitrary and capricious because it further this unlawful approach to the statute.

66. Under a correct construction of § 503B, sodium thiosulfate qualifies as an active drug ingredient for which there is a clinical need.

67. FDA's decision not to include sodium thiosulfate on the clinical need list violates the APA and should be set aside.

SECOND CAUSE OF ACTION
(Agency Action Unlawfully Withheld or Unreasonably Delayed in Violation of APA)

68. The above paragraphs are hereby incorporated by reference as if set forth fully herein.

69. FDA has unreasonably delayed listing active ingredients of FDA-approved drugs on the Section 503B clinical need list.

70. The DQSA, which Congress enacted more than a decade ago, contemplated that FDA would, in potentially a single regulatory action, list "drug substances for which there is a clinical need." 21 U.S.C. § 353b(a)(2).

71. FDA has no discretion to determine that there is not a clinical need for bulk drug substances that (1) are active ingredients in approved drugs that FDA has already determined are safe and effective and (2) are in current or historical demand in clinical treatment. Accordingly, the DQSA requires FDA to list such drug substances on the Section 503B clinical need list.

72. FDA's failure to do so harms Plaintiff FarmaKeio Outsourcing. FarmaKeio Outsourcing would compound from such bulk drug substances. But FDA's delayed and withheld action in completing the list required under the Clinical Need Condition has foreclosed FarmaKeio Outsourcing from compounding from such bulk drug substances.

73. Consequently, FDA has unreasonably delayed listing such bulk drug substances on the Section 503B clinical need list, and the Court should compel FDA to undertake the listing procedures of 21 U.S.C. § 353b(a)(2)(a)(i) respecting such bulk drug substances.

Prayer for Relief

Plaintiff respectfully requests that the Court enter judgment in its favor and that they be granted the following relief:

A. Declare that FDA's decision not to include sodium thiosulfate on the clinical need list is arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law;

B. Set aside and/or vacate FDA's decision not to include sodium thiosulfate on the clinical need list;

C. Remand to FDA for reconsideration of whether to include sodium thiosulfate on the clinical need list based on a correct reading of the relevant legal provisions;

D. Compel FDA to undertake the listing procedures of 21 U.S.C. § 353b(a)(2)(a)(i) for bulk drug substances that (1) are active ingredients in approved drugs that FDA has already determined are safe and effective and (2) are in current or historical demand in clinical treatment; and

E. Grant Plaintiff such other relief as may be necessary or appropriate or that the Court deems just and proper.

Dated: October 25, 2024

/s/ Ty Doyle

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